Interferon alfa-n1, Lymphoblastoid
WELLFERON® Injection

DESCRIPTION: WELLFERON (Interferon alfa-n1, lymphoblastoid) is a sterile protein product in aqueous solution for use by subcutaneous (SC) or intramuscular (IM) administration. WELLFERON is a mixture of alpha-interferons isolated from a human lymphoblastoid cell line following induction with murine parainfluenza virus type 1 (Sendai strain) and purified by immuno-affinity chromatography. Each of the nine predominant subtypes of alpha-interferon in WELLFERON consists of 165 or 166 amino acids and has a molecular weight (MW) of approximately 20,000 Daltons.

The lymphoblastoid cell and virus banks have been qualified, and the production process validated to inactivate or remove known adventitious viruses and microorganisms. Lymphoblastoid cell culture is carried out in medium containing polymyxin B and neomycin sulfate, although these antibiotics are not detectable in the final product. The purification procedure includes two immuno-affinity chromatography steps using bovine and ovine antibodies. Not more than 2.5 ng/megaunit (MU) of the antibodies is detected in the purified bulk blend.

WELLFERON is formulated with tromethamine/glycine-buffered saline (8.50 mg/mL sodium chloride, 0.75 mg/mL glycine, 1.21 mg/mL tromethamine, and Water for Injection). Human albumin is added as a stabilizer to give a total protein concentration of 1.5 mg/mL. It is a sterile, clear, colorless solution adjusted to pH 6.8 to 7.2 with hydrochloric acid or sodium hydroxide. WELLFERON contains no preservatives.

Each single-use vial contains 3 MU (3 million international units [IU]) of interferon antiviral activity in 1 mL. The specific activity of interferon alfa-n1 is not lower than 110 MU/mg interferon protein and not higher than 285 MU/mg.

CLINICAL PHARMACOLOGY: General: Natural alpha-interferons are produced primarily in leukocytes, bind to a high-affinity type I receptor, and have immunomodulatory, antiviral, and antiproliferative activities. Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that result in the induction of certain enzymes, inhibition of virus replication, suppression of cell proliferation, enhancement of the phagocytic activity of macrophages, and augmentation of lymphocyte cytotoxicity. The precise mode of action of alpha-interferons in the treatment of chronic hepatitis C, however, has not yet been determined.
Pharmacokinetics: After a single subcutaneous 3- or 10-MU dose, mean peak serum concentrations of WELLFERON were 43 and 139 IU/mL, respectively, in both healthy subjects and cancer patients. Peak concentrations appeared to be proportional to dose. Bioavailability of WELLFERON after subcutaneous or intramuscular injection ranged from 40% to 100% for both routes of administration. The time to reach peak concentration (t_{max}) ranged from 6 to 9 hours and

the mean apparent elimination half-life was 7 to 10 hours. Peak serum concentration and area under the serum concentration curve of WELLFERON suggested no accumulation after repeated (three times weekly) dosing.

Clearance of interferons in humans is thought to occur primarily by renal and other cellular catabolism. The apparent plasma clearance of WELLFERON in humans following intravenous administration was 85 mL/min and was independent of dose. Liver metabolism and subsequent biliary excretion are considered minor pathways of elimination for alpha-interferons. Alpha-interferons are not cleared by hemodialysis.

Pharmacokinetic profiles of WELLFERON did not vary appreciably in subjects of different gender or age, and chronic renal failure does not affect serum levels. In pediatric patients, serum levels of WELLFERON similar to those in adults may be achieved if the dose is adjusted based upon body surface area.

CLINICAL STUDIES: The safety and efficacy of WELLFERON in the treatment of adult patients with chronic hepatitis C were evaluated in two randomized, controlled trials that enrolled a total of 1511 patients. The first of the two trials (Study 1, n = 440) compared four different regimens of WELLFERON administered subcutaneously: 3 MU three times per week (TIW) for 6 months, 5 MU TIW for 6 months, 3 MU TIW for 12 months, and 5 MU TIW for 12 months.[1] The second major trial (Study 2, n = 1071) compared treatment with WELLFERON and treatment with recombinant interferon alfa-2b, INTRON-A (INTRON-A is a registered trademark of the Schering Corporation), both given at 3 MU subcutaneously TIW for 6 months (24 weeks).[2] Patients were 18 to 65 years of age, were diagnosed by liver biopsy and by history of elevated serum alanine aminotransferase (ALT) levels for 6 months (Study 1) or additionally by the presence of hepatitis C antibodies (Study 2), and lacked evidence of decompensated liver disease or infection by hepatitis B virus. The primary measure of efficacy in these trials was sustained response (normalization of ALT levels lasting at least 1 year following treatment). Secondary measures of efficacy included assessment of clearance of serum hepatitis C virus (HCV) RNA.

A higher number of sustained responses were observed in patients treated with 3 MU of WELLFERON for 12 months than those treated for 6 months (see Table 1). Patients receiving 5 MU of WELLFERON did not have significantly higher sustained response rates than those receiving 3 MU of WELLFERON.

Table 1: Rates of ALT Normalization* at End of Treatment and 1 Year Posttreatment (Study 1)

	WELLFERON		
	3 MU TIW 12 Months (n = 110)	3 MU TIW 6 Months (n = 113)	Difference (95% Confidence Interval)
End of Treatment	40.0%	35.4%	4.6% (-8.1, 17.3)
1 Year Posttreatment	19.1%	6.2%	12.9% (4.3, 21.5)

* ALT normalization was defined as serum ALT within the normal range at a single time point. Patients had sustained ALT response if they achieved ALT response at end of treatment, had a normal ALT value at 1 year posttreatment, and did not relapse (defined as two or more consecutively elevated ALT values) at any time between these measurements.

In Study 2, end-of-treatment response rates were similar between patients treated with 3 MU of WELLFERON and with 3 MU interferon alfa-2b (35.3% vs 37.9%). The sustained response rates for WELLFERON and INTRON-A were 10.3% and 6.7%, respectively, (95% confidence interval of the difference = 0.3%, 7.0%). It is now known for both agents that 6 months of therapy yields fewer durable responses than does more prolonged therapy.

Normalization of ALT values was first observed by Week 16 in 90% or more of patients who had ALT response at end of treatment.

Analysis of the subgroup of patients (n = 731, 68% of total) from Study 2 for which PCR results were available showed that subjects who received 3 MU TIW of WELLFERON for 6 months had a virologic response rate of 17.3% (95% confidence interval = 12.8%, 21.8%) 1 year after therapy, as determined using an unvalidated RT-PCR assay. The study results suggested a correlation between sustained normalization of serum ALT levels and clearance of detectable serum HCV RNA at the end of posttreatment observation.

A retrospective analysis of a subgroup of patients from Study 2 who had paired liver biopsy data (40% of total population) suggests a correlation between reductions in serum HCV RNA levels as measured by the polymerase chain reaction, normalization of serum ALT levels, and histologic improvement.

Immunogenicity: Serum antibody levels to alpha-interferon were measured in 403 of 440 patients in Study 1 using both an interferon-binding immunoassay and an assay to detect neutralizing antibodies for interferon-induced viral interference activity *in vitro*. Only 1/403 patients (<1%) had WELLFERON neutralizing antibody pretreatment with 27/403 patients (6.7%) testing positive by month 12. Sustained normalization of ALT was achieved in patients who either developed or did not develop detectable antibodies to interferon. The study was not adequate to determine if the development of neutralizing antibodies impacts response rates.

INDICATIONS AND USAGE: WELLFERON is indicated for the treatment of chronic hepatitis C in patients 18 years of age or older without decompensated liver disease. Appropriate testing should

be performed to establish the diagnosis of chronic hepatitis C. Other causes of hepatitis, including hepatitis B, should be excluded prior to therapy with WELLFERON.

CONTRAINDICATIONS: WELLFERON is contraindicated in patients with known hypersensitivity to alpha-interferons or any component of the product. The product is also contraindicated in patients who have a history of anaphylaxis to bovine or ovine immunoglobulins, egg protein, polymyxin B, or neomycin sulfate.

WARNINGS: Treatment with WELLFERON should be administered under the guidance of a qualified physician, and may lead to moderate to severe adverse experiences requiring dose reduction, temporary cessation, or discontinuation of further therapy (see DOSAGE AND ADMINISTRATION).

WELLFERON SHOULD BE ADMINISTERED WITH CAUTION TO PATIENTS WITH PRE-EXISTING CARDIAC DISEASE. Pre-existing cardiac illness could be exacerbated by therapy with alpha-interferons. Hypertension and supraventricular arrhythmias, chest pain, and myocardial infarction have been associated with interferon therapies. Hypotension has occurred in patients receiving WELLFERON and other recombinant products, most frequently when higher doses or intravenous doses are used. Patients with pre-existing cardiac disease should have electrocardiograms taken prior to and during the course of treatment.

DEPRESSION AND SUICIDAL BEHAVIOR INCLUDING SUICIDAL IDEATION, SUICIDAL ATTEMPTS, AND COMPLETED SUICIDES HAVE BEEN REPORTED IN ASSOCIATION WITH TREATMENT WITH ALPHA-INTERFERONS, INCLUDING WELLFERON. Caution should be used in treating patients with clinically significant, pre-existing depressive disorders, as such patients may be prone to more severe treatment-associated depression. Psychiatric monitoring is recommended for patients reporting psychiatric symptoms or for patients with a history of psychiatric disorders.

Central nervous system (CNS) adverse events associated with alpha-interferon therapy are diverse, generally transient, and reversible upon discontinuation of therapy. Occasionally seizures and coma or obtundation have been reported in patients receiving alpha-interferon therapy.[3] Additionally, CNS reactions include decrease in mental status, dizziness, impaired memory, agitation, manic behavior, and psychotic reactions.

WELLFERON should not be administered to patients with decompensated liver disease or autoimmune hepatitis because of the potential of treatment-related exacerbation of disease symptoms. Patients with signs of decompensated liver disease before treatment with alpha-interferons have shown clinical deterioration sometimes resulting in death during treatment.

Serious acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely following treatment with interferons. Treatment with

WELLFERON should be discontinued and appropriate therapy should be administered if these symptoms occur.

Infrequent reports of endocrine abnormalities are associated with alpha-interferon therapy. Development or exacerbation of pre-existing diabetes mellitus may occur. Thyroid abnormalities, including abnormal laboratory values and clinical hypo/hyperthyroidism may occur, and patients on treatment should have ongoing evaluation of thyroid/hormone axis. Patients should have therapy discontinued if endocrine abnormalities develop. Therapy may resume if endocrine symptoms abate, although endocrine abnormalities may not always be reversed after discontinuation of alpha-interferons.

Rare cases of autoimmunity including vasculitis, Raynaud's, rheumatoid arthritis, lupus erythematosus, and rhabdomyolysis have been reported during treatment with interferon. One pediatric patient with respiratory papillomatosis who received WELLFERON for approximately 7 years developed systemic lupus erythematosus (SLE) that resolved after discontinuation of WELLFERON and appropriate treatment.[4]

Retinal hemorrhages, cotton-wool spots, and retinal artery or vein obstruction have been observed rarely in interferon-treated patients.

PRECAUTIONS: General: Most serious and non-serious adverse reactions are reversible when detected early. If severe reactions occur, the drug should be discontinued and appropriate corrective measures be taken according to the clinical judgment of the physician (see DOSAGE AND ADMINISTRATION). If necessary, reinstitution of treatment with WELLFERON can be undertaken with caution.

Caution should be exercised when administering WELLFERON to patients with the following conditions:

- severe pre-existing autoimmune, renal, or hepatic disease; seizure disorders; and/or compromised central nervous system function.
- leukopenia or thrombocytopenia or who are concurrently receiving myelosuppressive agents.
- pulmonary dysfunction including unstable asthma or other conditions. Respiratory impairment is rare, but may be worsened in alpha-interferon-treated patients.

Elevated hepatic transaminases can occur following the administration of WELLFERON or other alpha-interferons. The degree of hepatotoxicity is modest in most patients but can be severe, particularly in patients with decompensated liver disease.

Treatment with WELLFERON is associated with thrombocytopenia, decreases in mean values for white blood cell (WBC) count and absolute neutrophil count (ANC), leukopenia, and, very rarely, myelosuppression or leukocytosis. Hemoglobin and hematocrit may gradually decrease, usually not lower than 20% below baseline, over the course of therapy with WELLFERON.

In addition, interferons may exacerbate skin conditions that include but are not limited to dermatitis, cellulitis, and psoriasis.

Variation in dosage, routes of administration, and adverse reactions exist among the different brands of interferons. Different brands of interferon should not be used for a single treatment regimen.

Information for Patients: Because of the possibility of severe or even fatal adverse reactions to interferon therapy, patients should be informed of both the benefits and potential risks of treatment with WELLFERON.

When patients are advised by their physicians to administer WELLFERON by self-injection, adequate instruction in subcutaneous or intramuscular administration practices should be provided. Patients should be cautioned against reusing syringes and needles. If home use is prescribed, an appropriate Sharps container and proper instructions for the disposal of used syringes and needles should be supplied to the patient. Patients should be thoroughly instructed on needle, syringe, and container disposal procedures and should be advised of the importance of following correct disposal procedures. See WELLFERON Patient Information Sheet.

Patients should be advised that anti-inflammatory analgesics (e.g., acetaminophen or ibuprofen) may alleviate some of the discomforts associated with initial treatment with WELLFERON. Patients receiving WELLFERON should also be advised to stay well hydrated, especially during the initial stages of treatment.

Patients should be advised that treatment with WELLFERON has not been shown to reduce the risk of transmission of HCV to others through sexual contact or blood contamination.

Laboratory Tests: Baseline laboratory tests should be performed on all patients treated with WELLFERON. Deviation of greater than 10% change from baseline may be prodromal to further abnormalities and would necessitate further monitoring. A guideline for acceptable baseline values prior to initiation of treatment:

- Platelet count >75 x 10^6/L
- Hemoglobin concentration >100 g/L
- ANC <1500 x 10^6/L
- Serum creatinine concentration <180 μmol (<2.0 mg/dL) or creatinine clearance >0.83 mL/second (>50 mL/minute)
- Serum albumin concentration >25 g/L
- Bilirubin within normal limits
- Thyroid stimulating hormone (TSH) and T_4 within normal limits

Standard hematologic tests (including hemoglobin, complete and differential white blood cell counts, and platelet count) and liver function tests should be performed periodically while undergoing treatment with WELLFERON.

Patients with pre-existing cardiac disease should have electrocardiograms taken prior to and during the course of treatment.

Patients with pre-existing thyroid abnormalities may be treated if normal thyroid stimulating hormone (TSH) levels can be maintained by medication. Testing of TSH levels in these patients is recommended at baseline and every 3 months following initiation of therapy.

Drug Interactions: Data on the effects of WELLFERON on the cytochrome P-450 enzyme system are inconclusive. Caution should be exercised when coadministering WELLFERON with other drugs metabolized by these enzymes (e.g., myelosuppressive agents like vinblastin or zidovudine) or drugs with a narrow therapeutic index (e.g., theophylline).

Carcinogenesis, Mutagenesis and Impairment of fertility: WELLFERON has not been tested for its carcinogenic potential. WELLFERON was not mutagenic when tested in the Ames bacterial assay, using five different *Salmonella typhimurium* tester strains in the presence and absence of metabolic activation. Menstrual irregularities, including transiently decreased serum levels of progesterone and luteinizing hormones suggestive of anovulation, were observed in female Rhesus monkeys given daily subcutaneous injections of WELLFERON for 1 month at 45 to 240 times the recommended weekly human dose (based on surface area). A daily dose of 0.1 MU/kg (approximately 2.5 times the weekly human dose), however, had no effects on cycle duration or ovulation. The effects of WELLFERON on male fertility were not studied.

Pregnancy: Pregnancy Category C. Treatment with WELLFERON has been associated with embryolethal or abortifacient effects in Rhesus monkeys administered doses corresponding to approximately 11 to 55 times the cumulative weekly human dose (based on body surface area). These effects were observed regardless of whether WELLFERON was administered early or late during gestation. There are no adequate and well-controlled studies of WELLFERON in pregnant women. WELLFERON should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from WELLFERON, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of WELLFERON in pediatric patients have not been established.

Geriatric Use: Clinical studies of WELLFERON did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, treatment of elderly patients should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS: Flu-like symptoms, including asthenia, headache, fever, myalgia, chills, and nausea were the most frequent adverse experiences reported in both studies.

Adverse experiences that occurred in at least 5% of patients in Study 2 receiving 3 MU WELLFERON for 6 months are provided in Table 2. Adverse events reported in the 6 month and 12 month treatment arms of Study 1 were generally similar to those reported in Study 2.

Table 2: Incidence of Adverse Reactions Occurring in ≥5% of the Population

Adverse Event	WELLFERON 3 MU TIW 6 Months (n = 524)
Application site	
Injection site reaction (also includes pain, edema, hemorrhage, and inflammation of injection site)	21%
Body as a whole	
Asthenia	60%
Headache	52%
Fever	43%
Chills	31%
Pain	13%
Back pain	11%
Central nervous system/peripheral nervous system	
Dizziness (also includes vertigo)	9%
Impaired thought (includes confusion, abnormal thinking, and amnesia)	6%
Paresthesia (also includes hyperthesia)	5%
Gastrointestinal	
Nausea	23%
Diarrhea	13%
Abdominal pain	12%
Anorexia	8%
Vomiting	6%
Weight loss	5%
Musculoskeletal	
Myalgia	36%
Arthralgia	19%
Psychiatric	
Anxiety (includes nervousness, agitation, hostility, and emotional lability)	18%
Sleep disturbance (includes insomnia, somnolence, and sleep disorder)	14%
Depression	13%
Respiratory	
Pulmonary disorder (includes cough, bronchitis, dyspnea, pneumonia, and respiratory, lung, and pleural disorders)	7%
Rhinitis	7%
Pharyngitis	6%
Skin	
Alopecia	16%
Rash	8%
Dry skin (includes pruritus, dry skin, and urticaria)	8%
Sweat	5%

Serious and/or severe adverse events reported in less than 5% of patients in Studies 1 and 2 included altered hormone levels, amblyopia, arrhythmia, thyroid carcinoma, angina, hypo/hypertension, myocardial ischemia, cholecystitis, convulsions, cyst, peripheral edema, abnormal ejaculation, atrial fibrillation, hallucinations, herpes simplex, hyperglycemia, hypo/hyperthyroidism, urinary tract infection, accidental injury, decreased libido, abnormal liver

function, liver tenderness, migraine, peritonitis, pharyngitis, photosensitivity, psoriasis, ruptured spleen, retinal vein thrombosis, seizure, and suicidal behavior (ideation, attempts).

ABNORMAL LABORATORY TEST VALUES: Abnormal laboratory values were observed in patients in Study 2 receiving 3 MU of WELLFERON for 6 months as described below. Patients receiving 3 MU of WELLFERON for 12 months did not have, in general, more abnormal laboratory values than those receiving 6 months of therapy.

Platelets: 3% of patients experienced thrombocytopenia. 2% of these cases were classified as grade III or grade IV by WHO criteria.

WBC: 5% of patients experienced neutropenia. <1% of these cases were classified as grade III or grade IV by WHO criteria. 4% of patients experienced lymphopenia. 1% of these cases were classified as grade III or grade IV by WHO criteria.

Creatinine: 2% of patients experienced WHO grade I elevation of creatinine.

Thyroid: 3% of patients had laboratory abnormalities (including abnormal TSH and T_4).

Glucose: 5% of patients experienced hyperglycemia (blood glucose >120 mg/dL FBS).

OVERDOSAGE: Abnormal laboratory findings and side effects are generally increased proportionally to the dose of WELLFERON. Repeated large doses of alpha-interferons have been associated with profound lethargy, prostration, and coma. Neurotoxicity including EEG abnormalities and seizures have been observed with investigational high doses (100 to 200 MU). Repeated high investigational dosing of cancer patients with alpha-interferons (e.g., generally >15 MU/m^2, three times per week or more) has been associated with transient abnormalities in serum liver function tests, hyperkalemia, and renal consequences such as elevations of serum BUN and creatinine, proteinuria, nephrotic syndromes, renal insufficiency, and renal failure.[5,6]

DOSAGE AND ADMINISTRATION: The recommended dosage of WELLFERON for the treatment of chronic HCV infection is 3 MU administered subcutaneously or intramuscularly three times per week for 48 weeks (12 months). Patients who show no reduction in serum ALT or HCV viral load within the first 16 weeks of therapy are unlikely to benefit from continued treatment.

Patients who do not tolerate therapy should have their dose of WELLFERON interrupted or reduced by 50% until signs or symptoms resolve. Those who continue to not tolerate therapy after dose modification should discontinue therapy.

If home use is determined appropriate, instructions on use should be given by a health care professional. After administration of WELLFERON, it is essential to follow the procedure for proper disposal of syringes and needles. See the enclosed "Patient Information Sheet" for detailed administration instructions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If particulates or discoloration are observed, the container should not be used.

HOW SUPPLIED: WELLFERON Injection is supplied as a sterile injectable solution containing 3 MU in 1 mL of solution per vial. One MU (megaunit) is equal to one million international units (IU).

Boxes of three vials containing 3 MU of interferon alfa-n1 (3 MU/mL) (NDC 0173-0660-00).

STORAGE: Store in the refrigerator at 2 to 8°C (36 to 46°F) and protect from light. Do not freeze or shake vial.

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Patient Information Sheet - Save, Do Not Discard

Interferon alfa-n1, Lymphoblastoid
WELLFERON® Injection

Introduction
Please read this leaflet carefully before you use WELLFERON Injection. It provides a summary of the information available on your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on WELLFERON. For further information or advice, ask your doctor or pharmacist.

What's in your medication?
WELLFERON Injection (interferon alfa-n1, lymphoblastoid) has been prescribed for you by your doctor because you have chronic hepatitis C, caused by infection with the hepatitis C virus (HCV). Many patients with hepatitis C can be treated with interferons. Interferons are natural proteins produced by your body to help fight infections including viral infections such as HCV.

WELLFERON is a purified mixture of human alfa-interferons. WELLFERON comes in vials containing 3 megaunits (MU) of interferon in a sterile solution. Each vial contains 1 mL which is equal to one 3MU dose. WELLFERON also contains human serum albumin.

Storing your medication
Keep your WELLFERON in the refrigerator at 36 to 46°F (2 to 8°C). Do not freeze. Separate refrigerated medicines from food by keeping them in a plastic bag, container, or separate drawer. Keep medications and supplies away from liquid, heat, and direct sunlight. Check the expiration date on your vial of WELLFERON; if the expiration date has passed, do not use it and consult your pharmacist.

Take the vial(s) of WELLFERON out of the refrigerator 1/2 hour before your injection to bring the solution to room temperature.
Check medication vial(s) for:

- Expiration date
- Cracks, damage, particulate matter, and discoloration
- DO NOT USE CONTAMINATED, DAMAGED, OR EXPIRED VIALS!
- DO NOT SHAKE THE VIAL(S)!

R E M E M B E R:
This medication is for YOU. Only a doctor can prescribe it for you. Never give it to others even if their symptoms are the same as yours. It may harm them.

Keep your medication and administration supplies out of the reach of children.

WELLFERON® Injection
(Interferon alfa-n1, Lymphoblastoid)

Step 1:

Before using your medication answer the following questions:

The decision to use WELLFERON will be made by you and your doctor. These questions are important to consider before using WELLFERON. If the answer to any of the following questions is YES or if you do not know the answer, then please discuss with your doctor before you use WELLFERON.	YES	NO
• Have you previously experienced any unusual or allergic reaction to WELLFERON or another interferon?		
• Have you recently taken, are you currently taking, or are you likely to be taking **any** prescription or over-the-counter medicines while you are using WELLFERON?		
• Are you asthmatic?		
• Are you of childbearing age, sexually active, and are you practicing safe sex?		
• Are you pregnant, trying to become pregnant, or breast feeding?		
• Do you suffer from thyroid, heart, kidney, central nervous system disease (e.g., seizures, nervousness, dizziness), or a liver disease other than HCV?		
• Do you suffer from, or have you ever experienced depression, felt excessively sad, or had suicidal thoughts?		
• Do you suffer from any bleeding problems?		
• Do you have diabetes mellitus (sugar diabetes)?		

If the answer is YES to any of these questions, and if you have not already discussed them with your doctor, tell him/her before you use your medication.

What you should know before using WELLFERON

- Treatment with WELLFERON has not been shown to reduce the risk of transmission of HCV to others through sexual contact or blood contamination.
- It is important to use your medication at the times directed by your doctor. The label from the pharmacy will tell you how much to use and how often. If it doesn't or you are not sure, ask your doctor or pharmacist.
- If you miss a dose of WELLFERON, check with your doctor for further instructions. The flu-like side effects of interferons are often more noticeable when dosing is resumed after missed doses.
- Discuss the use of any other medications (prescription or over-the-counter), drugs, and alcohol with your doctor.
- During your course of treatment, your doctor will want you to have periodic blood tests to check the blood cell counts and blood chemistries reflecting kidney and liver functions.
- Interferons may cause you to be more tired or dizzy. Exercise caution when operating machinery or driving a motor vehicle.
- Your doctor and/or nurse will have shown you how to inject your medication. If you are unsure of the procedure, check with your doctor or nurse.
- The injection is given into the layer just below the surface of the skin or into a muscle. (See detailed instructions below under Directions for Administration.)
- Do not inject WELLFERON into a vein.

- Once you start treatment with WELLFERON, do not switch brands of interferons without first consulting your doctor.

Side effects of your medication

Along with its intended effects, WELLFERON may cause some unwanted effects. Although not all of these side effects may occur, if they do occur, you may need medical attention. Some of the side effects that might be expected, and what can be done to help them, are shown below:

Common side effects:	**Uncommon side effects:**
• Flu-like symptoms (e.g., chills, fever, weakness, tiredness, muscle aches, nausea, and headache). In order to minimize flu-like symptoms, inject your medication in the evening. Your doctor may advise you take acetaminophen or ibuprofen, drink plenty of fluids, and get plenty of rest. • Poor appetite. Avoid foods that upset your stomach, select foods you enjoy eating and make sure you eat at least 3 times a day. • Weight loss. • Increased need for sleep. • Anxiety, mild depression, nervousness, and confusion. • Hair loss. • Change in blood sugar levels if you are a diabetic. • Dry skin, rash and itching.	• SEVERE DEPRESSION AND SUICIDAL IDEATION AND SUICIDE ATTEMPT. • DIZZINESS, FEELING FAINT, RACING HEART (PALPITATIONS), CHEST PAIN, OR OTHER HEART SYMPTOMS. • Anemia (leading to tiredness). • Sore throats, mouth ulcers, and other infections. • Increased risk of bruising and bleeding (e.g., nose bleeds). • Diarrhea. • Unexplained swelling of hands, feet, and/or face. • Blood in the stool or urine. • Painful or less frequent urination. • Coldness of the fingers or toes.

If any of these or any other unusual effects occur, or if you feel unwell in any other way, contact your doctor.

Step 2: Preparing for Administration

1. Gather supplies. Remember to take your dose of WELLFERON out of the refrigerator 1/2 hour before using.
2. Clean work area.
3. Wash hands thoroughly with soap and water.
4. Remove cap from vial.
5. Clean top of vial with an alcohol swab.
6. Open syringe.
7. Pull syringe plunger back to line on syringe which corresponds to amount of drug to be given (this will usually be 1 cc. **Note:** 1 cc = 1 mL).
8. Remove needle cap from syringe.
9. Insert needle into the top of the vial.
10. Inject air from empty syringe into the air space above the liquid in the vial.
11. Turn syringe and vial upside down (See Figure 1).
12. Fill syringe with medication by pulling the plunger back while the needle is in the liquid. Do not pull the plunger all the way out of the syringe.
13. Remove syringe from vial. Hold syringe so that needle points upward.
14. Gently tap syringe with forefinger to force air bubbles in the fluid to the top of the syringe.
15. Advance plunger to number equal to amount of medication to be given (usually 1 cc). Recap needle.
16. Cleanse the injection site with an alcohol swab in an outward circular motion. Repeat with another alcohol pad. Let the site dry for a few seconds.
17. Uncap the needle. **Do not let the needle touch anything.**

Medication and Supplies

- WELLFERON - 1 mL vials.
- Syringes - Different syringes and needles are used for the two different methods of injection. Your doctor will explain to you which method and what size syringe and needle to use.
- A sharps container for collecting used syringes and needles.
- Alcohol swabs (pads).

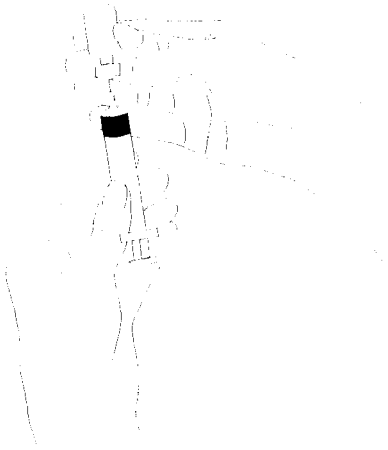

Figure 1

Step 3: Injection Site Selection

This guide is designed to help you feel comfortable with subcutaneous (underneath the skin) or intramuscular (into the muscle) injections. Please refer to this guide for general information. If you have any questions, please consult your doctor.

Each time an injection is given, a new site should be used. Alternate between the right and left arms and legs (or sides of the body), or abdomen. It is important to distinguish between sites appropriate for subcutaneous (Figure 2) and intramuscular (Figure 3) use.

For Subcutaneous Use

Choose an injection site - upper arm, abdomen (except navel or waist), or upper thigh. (See Figure 2).

Figure 2

For Intramuscular Use

Choose an injection site - upper arm, buttocks, or thigh. (See Figure 3).

Figure 3

For Subcutaneous Use

1. Pinch the skin firmly between your thumb and forefinger (See Figure 4.)

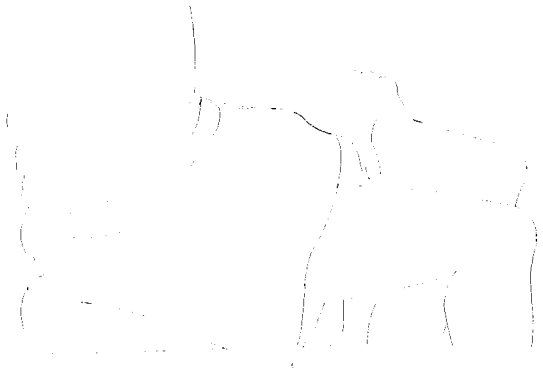

Figure 4

2. Position bevel (opening) of needle facing up (See Figure 5).
3. Insert needle straight into the clean site at a 45° to 90° angle as far as it will go (See Figure 5).

Figure 5

4. Release grasp of skin and pull back slightly on the plunger. If any blood enters the syringe, withdraw the needle. Dispose of needle, syringe, and medicine in the syringe by placing in the collection container. Start again with a new needle, syringe, and medicine injecting at a different site. If no blood is present in the syringe, inject the medicine by pressing the plunger into the syringe all the way in. ALWAYS WITHDRAW THE NEEDLE AT THE ANGLE IT WAS INSERTED (See Figure 6).

Figure 6

5. After removing the needle, place an alcohol swab over the injection site and gently rub for a few seconds.

For Intramuscular Injection

1. With one hand, stretch the skin around the injection site so it is taut. (See Figure 7.)

Figure 7

2. Hold syringe with other hand, making sure it is horizontal until ready for injection.
3. Insert needle at a 90° angle with a quick dart-like thrust. Expect to feel some resistance. (See Figure 8.)

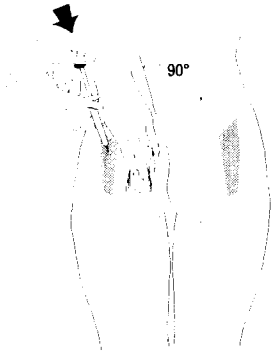

Figure 8

4. Release grasp of skin and pull back slightly on the plunger. If any blood enters the syringe, withdraw the needle. Dispose of needle, syringe, and medicine in the syringe by placing in the collection container. Start again with a new needle, syringe, and medicine injecting at a different site. If no blood is present in the syringe, inject the medicine by pressing the plunger into the syringe all the way in. ALWAYS WITHDRAW THE NEEDLE AT THE ANGLE IT WAS INSERTED
5. After removing the needle, place an alcohol swab over the injection site and gently rub for a few seconds.

Disposal of Syringe and Needle

Dispose of syringes and needles as directed by your doctor, nurse, or pharmacist or by following these steps:

- A sharps or other appropriate container can be obtained from your pharmacist.
- Place all used needles and syringes in an appropriate sharps container with a lid. Do not use glass or clear plastic containers, or any container that will be recycled or returned to a store. Always store the container out of the reach of children.
- Properly label the container to indicate its contents.
- When the container is full, check with your doctor, nurse, or pharmacist regarding appropriate disposal. There may be special state and local laws that apply.
- ***Use each needle and syringe only once.***
- **Do not allow anyone else to use your needles or syringes! Many diseases can be spread by the sharing of used syringes and needles.**

Storage: Refrigerate at 2 to 8°C (36 to 46°F) and protect from light. DO NOT FREEZE.

WELLFERON® Injection
(Interferon alfa-n1, Lymphoblastoid)

Please note that the information included in this leaflet is not intended to be full disclosure of all known warnings and precautions or possible effects of WELLFERON. Additional information is included in the WELLFERON package insert and you should discuss any questions with your doctor.

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